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EXAMINER	
MARVICH, MARIA	

ART UNIT	PAPER NUMBER
1633	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/764,628	TROCHON ET AL.	
	Examiner	Art Unit	
	MARIA B. MARVICH	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *7/6/10*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13,17,21 and 25-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13,17,21 and 25-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *1/26/04* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This action is in response to an amendment filed 7/6/10. Claims 13, 17, 21 and 25-30 are pending in this application.

Applicants' amendment has been sufficient to overcome the previous objections to the claims. However, the following informalities were noted.

Claim Objections

Claims 13, 17, 21 and 26 are objected to because of the following informalities: **These are new objections.** Claim 13 is drawn to administration of an expression plasmid coding for a therapeutic peptide and in line 8 that the " therapeutic peptide is encoded by a polynucleotide sequence". However, there is no direct indication that the polynucleotide is on the plasmid. For clarification it would be remedial to amend line 5 to recite, --of an expression plasmid comprising a polynucleotide-- and to delete in line 7-8 --where the therapeutic peptide is encoded by a polynucleotide and to state, --wherein the polynucleotide sequence is operably linked to--. The same amendment is recommended for claims 17 and 21.

Secondly, claim 13 recites that the administration is to an intramuscular or intratumoral site followed by electric pulse to "a corresponding intramuscular or intratumoral site(s)". It is not clear to what the sites correspond. It appears as if particular sites are injected and then these sites receive electrical pulses. It would, if this is the case, be remedial to recite, --followed by application of electric pulses to the injected intramuscular site or the injected intratumoral site--. This objection also stands for claims 17 and 21.

Claim 26 recites "a therapeutic peptide consisting of SEQ ID NO:1" which should be amended to recite --the therapeutic peptide consisting of SEQ ID NO:1-- as it is proper to use the article "the" when referring to previously recited limitations.

Appropriate correction is required.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 13, 17, 21 and 25-30 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of direct injection *intratumorally* to a melanoma or a pulmonary metastasis of an expression plasmid comprising a polynucleotide coding for a therapeutic peptide consisting of an amino acid with the sequence of SEQ ID NO:2 wherein the polynucleotide is operably linked to an expression control sequence, followed by application of electric field pulses to the melanoma or the pulmonary metastasis wherein expression of SEQ ID NO:2 results in the decrease in the number of new intratumoral vessels and in inhibition of growth of the melanoma or inhibition of the pulmonary metastases, does not reasonably provide enablement for any other embodiment. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. **This rejection is maintained for reasons set forth 7/9/08 and 4/15/09 and restated below. The rejection has been slightly reworded based upon applicants' amendment.**

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation (*United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is required is not based on a single factor but is rather a conclusion reached by weighing many factors (See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter, 1986) and In *re Wands*, 8USPQ2d 1400 (Fed. Cir. 1988); these factors include the following:

The instant claims are drawn to a methods of decreasing the number, or formation of intratumoral vessels in a mammal, in a mammal with melanoma and in a mammal with pulmonary metastases by direct inoculation and electrotransfer of a nucleic acid consisting of the polynucleotide sequence of SEQ ID NO:1 operably linked to an expression control sequence. The specification teaches that the disintegrin domain of metargidin when delivered to a tumor or metastases site can cause a diminution of vessels and thus lead to a decrease in pulmonary metastases and melanoma growth. The method recites quite broadly that the nucleic acid is delivered by electrotransfer to an intramuscular site or an intratumoral site. First, it is not clear what relationship the intratumoral site or intramuscular site have to the intratumoral vessels. Hence, the nucleic acid is introduced intramuscularly or intratumorally but if this site is to be adjacent or consistent with the intratumoral vessels is unclear. This leads to issues of unpredictability described more completely below. Briefly, gene therapy is hindered by methods of introduction that are not direct. Secondly, while the claims recite that the disintgerin domain "consists" of SEQ ID NO:1, this does not limit the context into which the sequence can be found.

This is exacerbated by the recitation that the plasmid is injected intratumorally or intramuscularly followed by electrical pulses. Furthermore, claim 26 recites that the plasmid is "administered by intramuscular or intratumoral injection followed by application of electrical pulses to an intramuscular site in the mammal" appears to recite that the expression plasmid can be introduced intramuscularly or intratumorally but the electrical pulse is only intramuscular. As expounded further below, it is not clear that the specification supports such breadth nor that all components of such method steps are enabled. The art teaches direct administration of genes for adequate expression levels which limits the enabled route of administration to **the intratumoral site** emphasis provided as the claims do not limit the intratumoral site to one located near the target tumor. And the specification only teaches administration of electric shock to the mouse as well as electrotransfer in mouse muscle (see e.g. ¶ 0095 and 120). It is not clear, given that mouse models do not extrapolate well to human subjects and the art of electrotransfer is unpredictable (see below).

The disintegrin domain constitutes Met 420 to Gly 511 of the full-length metargidin. However, SEQ ID NO:1 does not encode all of the metargidin. Rather, SEQ ID NO:1 encodes **the** disintegrin domain of metargidin and this disintegrin domain is encoded by all of SEQ ID NO:1. The specification states that metargidin comprises AMEP (anti-angiogenic metargidin peptide) and is a human protein with multipotent function including blocking angiogenic functions of integrin alpha v beta, inhibition of migration and formation of capillary structures and functions proapototically independent of modification of their cell cycle. Metargidin is a member of the adamalysin family (ADAMS) which functions in proteolysis, adhesion, fusion and intracellular signaling (see Ruben et al, US 2002/0182702 ¶ 1042). Multiple ADAMS have

been identified including ADAM1, ADAMTS-1, fertilin (ADAM2), cryitestin (ADAM3), epididymal apical protein I, meltrin, MS2, TNF-a converting enzyme, Kusbanian and metargidin (see Ruben et al, ¶ 0004). Within the ADAMS, the disintegrin domain functions to prevent integrin-mediated cell to cell and cell to matrix interactions such as plated aggregration, adhesion, migration of tumor cells or neutrophils or angiogenesis. There have been multiple propositions that members of the adamalysin family have a potential to treat a myriad of conditions such as those recited here (see Ruben et al US 2002/0165377 and Young et al (US 2003/0194797 in which the role of ADAM-22 and any other ADAM protein in inhibiting angiogenesis or invasion or formation of metastases, treating cancer, treating inflammatory diseases, treating atherosclerosis, treating macular degeneration or treating psoriasis is proposed), but these propositions have not lead to the identification of any treatments that are viable options against diseases. Applicants synthesize AMEP in bacteria and demonstrate that this protein can function to inhibit adhesion of fibrinogen to vitronectin and fibronectin, inhibit endothelial cell migration, proliferation, capillary formation and stimulates proapoptosis in endothelial cells *in vitro*. *In vivo,* AMEP nucleic acid was electrotransferred to muscle of nude and C57B1/6 mice and inhibited growth of MDA-MB-231 tumor growth and formation of pulmonary metastases in syngeneic mice.

The MPEP teaches, "However, claims reading on significant numbers of inoperative embodiments would render claims non-enabled when the specification does not clearly identify the operative embodiments and undue experimentation is involved in determining those that are operative. Atlas Powder Co. v. E.I. duPont de Nemours & Co., 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984); In re Cook, 439 F.2d 730, 735, 169 USPQ 298, 302 (CCPA 1971).

(see MPEP 2164.08(b)." First, the claimed method steps require direct inoculation and electrotransfer to an intramuscularly or intratumorally site. In this case, the claim does not set forth the relationship of the site of inoculation and the target site. For example, to what the inoculation is direct. As well, it is not clear what steps of the method of "direct inoculation and electrotransfer" are as disclosed by the specification. There is a single example of electrotransfer in ¶ 0095 wherein the plasmid is injected into the tibia cranial muscle of mice and following that 8 electric shocks of 200 V/cm were applied to the mouse. Hence, the specification teaches, injection intramuscularly followed by application of electric shock to electrotransfer the plasmid DNA into the muscle cells. This method is supported by Mir which teaches that the DNA must be injected into the tissue followed by delivery of electrical pulses to the target tissue, the order cannot be reversed (see page 169, col 2) that is strictly local (see e.g. page 170, last ¶). Local transfer is required as concentration of DNA is low and thus is sensitive to dilution (see page 171, ¶ 2) and thus injection and electric pulses must be limited to the target site.

Further regarding methods of transfer, the art teaches that the method of delivery of polynucleotides is highly unpredictable to date. Gene delivery has been a persistent problem for gene therapy protocols and the route of delivery itself presents an obstacle to be overcome for the application of the vector therapeutically. In fact, the specification teaches, "Likewise, most transgenic protein expression is mostly, though not exclusively, restricted to the injection site. Such experiments have failed to demonstrate widespread expression of transgenic proteins in the brain beyond two months". As well, Verma et al (Verma and Somia, Nature, September 1997) teach, "The Achilles heel of gene therapy is gene delivery.., the problem has been an inability to deliver genes efficiently and to obtain sustained expression". The unpredictability associated

with viral based therapies has been recently highlighted in the art, see for example, Check, Nature, 2003. Leakiness of and dissemination to tissues surrounding the targeted area and hence expression of receptor in non-targeted cells is particularly lethal, "dissemination of the vector particle itself can have harmful consequences; lack of adenovirus vector specificity was directly linked to the induction of the massive systemic immune response that caused the death of Jesse Gelsinger in 1999 (see Thomas page 354, col 1). Even use of tissue specific or inducible promoters cannot offset these ill effects. Vector tropism, the duration of transgene expression and vector immunogenicity are other factors that influence the suitability of a vector for specific therapeutic applications (see Thomas, page 348, col 2). "Lentiviral transduction of muscle and liver has also been shown in animals, but, interestingly, studies in the liver have indicated that not all non-dividing cells are equally susceptible to transduction by lentivirus vectors; some cell types (such as the hepatocyte) might require cell cycling for efficient gene transfer in vivo (see Thomas, page 348, col 2)." To date, no single mode of gene transfer has provided a viable option for successful gene therapy protocols. In more advanced studies related to cancer, the art teaches "to bring about a desired therapeutic outcome. Reasonably accurate gene delivery can be achieved by direct inoculation of plasmids or recombinant viruses using a needle position in a tumour deposit." (Russell page 1165, col 2,¶ 4-5).

Furthermore, in vitro and animal models have not correlated well with in vivo clinical trial results in patients. It is not clear that reliance on experimental models accurately reflects the relative superiority or efficacy of the claimed therapeutic strategy and applicants present no disclosed or art recognized nexus between the xenograph and nude mice experimental models and the human disease state. "Although animal studies have suggested low toxicity and excellent

efficacy, these investigation have been limited by the use of immuno- deficient mice" (Meng and Diery p. 6, column 1). The success of any in vitro assays or in vivo animal models cannot be considered as evidence of success of treatment, in vivo results rarely correlate well with in vivo clinical trial results in patients and have not translated into successful human therapies. Many in vitro and animal models that are provided as evidence of success of treatment have not translated into successful treatments in humans. Ultimately the mouse model predicts agents that are effective in treating mice but not humans (see Gura, e.g. page 1041, col 1 and col 2, last paragraph). Therefore, the ability to predict potential success in humans based upon experimental results is highly unpredictable as demonstrated by the art. Rather for humans direct administration appears necessary to reduce non-desirable effects as well as to ensure full effect of delivered biomolecules

The invention recites use of a direct inoculation and electrotransfer of nucleic acid encoding the disintegrin domain to any muscle or tumor to decrease the number of formation of intratumoral vessels in a mammal. Given the unpredictability of the art with regard to nucleic acid stability once administered, the lack of adequate working examples and the lack of guidance provided by applicants, the skilled artisan would have to have conducted undue, unpredictable experimentation to practice the claimed invention.

Response to Amendments

Applicants' response filed on 7/6/10 has been considered but is not persuasive for the following reasons. Applicants' arguments have been based in part on a Declaration co-filed with the response. The Declaration under 37 CFR 1.132 filed 7/6/10 is insufficient to overcome the

rejection of claims based upon 112 first paragraph as set forth in the last Office action because: of reasons set forth below.

The claims have been rejected under 35 USC 112, first paragraph as a number of embodiments within the scope of the claims carry with them a great deal of unpredictability, this is coupled with the highly unpredictable nature of the art and exacerbated by the lack of clarity in the claims. The claims are drawn to treatment in a mammal the method comprising administration to an intramuscular site or an intratumoral site of an expression plasmid that comprises, apparently, a polynucleotide that encodes a therapeutic peptide consisting of SEQ ID NO:2. Following this, an electrical pulse is administered at a copending intramuscular site or an intratumoral site. Applicants have classified the rejection as comprising three parts, route of administration, site of administration and lack of *in vitro* clinical trials. The later characterization is in contrast to the intended issues set forth in the rejection. As an aside, it is not clear what is encompassed by *in vitro* clinical trials. However, more to the point, the lack of clinical trials is not at issue. Rather, the lack of experimental results only affects the invention dues to the high degree of unpredictability related to this art. The lack of results supports a stance that the methods cannot be performed as recited. In other words, if these methods as recited were successfully performed using different nucleic acids for similar outcomes or using similar methods that would demonstrate a means of overcoming obstacles that historically prevent the method from working.

Dealing with the unpredictability related to gene therapy, the method engages techniques that have been deemed highly unpredictable in the art as detailed above. Specifically, the methods of delivery must ensure that the target is adequately provided nucleic acid sequence and

must avoid ancillary effects that are not desired in surrounding areas as well as loss of functionality of the nucleic acid due to dissemination of the nucleic acid from the target site. Applicants have amended the claims to indicate that the nucleic acid is administered by direct injection and electrotransfer intramuscularly or intratumorally. Applicants argue that the scope of the claims as recited is consistent with the rejection. However, the rejection states that the nucleic acid is not directly administrated to tumor, the melanoma or the pulmonary metastasis wherein the instant claims have no requirement that the site of inoculation is directly inoculated. It is noted that the rejection did not reference "inoculation" but rather administration or more specifically injection. The rejection sets forth that intratumoral injection will ensure delivery of the nucleic acid to the target and intramuscular injection will not. It is accepted that direct injection of DNA will reduce the dilution of the sequence such that therapeutic levels of peptide can be achieved without harmful affects of vector encountered when the delivery is not local. In fact, Mir teaches methods of delivering nucleic acid by electrotransfer to muscles for the express goal of treating muscular diseases,

> Electrotransfer allows modulation of foreign gene expression by varying either the amount of DNA injected, electric-pulse parameters, and/or the volume of tissue exposed to the electric pulses. **Only local effects were obtained,** in agreement with the known local permeabilizing effects of appropriate electric pulses (35, 37–39). These various control levels permit adjustment of foreign gene expression to achieve the desired investigative or therapeutic goal.

The results provided by applicant during prosecution history are not in contrast to the rejections. Applicants provide the following results

1) Trochin-Joseph electrotransfer of the AMEP into mouse skeletal mice *in vivo* leads to rapid, stable and tightly regulated expression of the transgene suggested that a producer cell can be distant from the target.

2) The specification teaches, AMEP nucleic acid was intramuscularly injected and electrotransferred leading to expression in the muscle of nude and C57B1/6 mice, which inhibited growth of MDA-MB-231 tumor growth and inhibited formation of pulmonary metastases in syngeneic mice

3) The Declaration filed 5/8/07 teach that AMEP nucleic acid was intratumorally injected and then electrotransferred and expressed in the muscle of nude and C57B1/6 mice inhibited growth of B16F10 and C0 melanoma tumor growth and this was correlated in the Declaration filed 7/6/10 to inhibited formation of pulmonary metastases.

Regarding the first result, applicants want to demonstrate that the AMEP molecule may act in trans as "the AMEP molecule only needs t be present in sufficient concentration in circulating blood". This accentuates the key issue of the rejection, adequate delivery to the target site must be. The art has concluded that the only way to ensure nucleic acid be delivered in adequate levels is by direct administration. And while this does not mean that each blood vessel must be injected, it does require injection of the intratumoral site. The second two results demonstrate that in animals, intratumoral and intramuscular injection leads to reduced tumor growth and to an inhibited formation of new vessels. The rejection argues that the later result may not be attainable in humans given the concerns of delivery methods wherein enough molecule must be received at the site without ancillary effects. Applicants argue that a number of results in animals including those set forth in the Declaration provide evidence of the operability

of the method. However, as set forth above, results in animals cannot be extrapolated with confidence to reflect predictable results in humans, who are the intended target for this method particularly in light of the lack of evidence that a method of injection to any intramuscular site will lead to levels at a desired target site *in trans* without extraneous deleterious effects.

Turning to the lack of clarity, in the claims, a number of objections are provided above regarding several aspects of the method. In addition, the target subject was called into question in the previous rejection wherein those of claim 17 and 21 have been clarified. However, claim 13 is not clear as to the subject treated by reciting "a mammal in need thereof". Such a subject encompasses a number of mammals that may or may not comprise a tumor given that a reasonable goal for any subject is to decrease formation of intratumoral vessels. However, it appears as if the method of claim 13 is intended to be a treatment for a mammal comprising a tumor wherein the treatment decreases the number or the new formation of intratumoral vessels. In each of claims 13, 17 and 21, the ability to decrease the presence of formed vessels seems implausible given the details in the specification and also what is known in the art relating to disintegrin function. In fact, as based upon applicants' arguments, the Declaration demonstrated intratumoral injection followed by electrotransfer of plasmid AMEP wherein the effect was measured as a decrease in tumor volume. Hence, the results are not commensurate in scope with the claims and do not demonstrate that the predictability of decreasing the number of already formed vessels lacks predictability is possible. This issue has been clarified by inserting the word "new" into the scope rejection above.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 13, 17, 21 and 25-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bettan et al (Bioelectrochemistry, 2000, pages 83-90; see entire document) in view of Fanslow et al (US 7,074,408; see entire document) and as evidenced by or further in view of Merkulov et al (US 6,294,368; see entire document). **This rejection is maintained for reasons set forth 4/15/09 and restated below. Bettan et al teach direct injection of the plasmid into the tumor or site of action and thus does not read on the non-enabled aspects as set forth above (see e.g. section 2.3, page 84). Hence, Bettan reads on the enabled scope of the claims.**

Applicants claim a method of decreasing intratumoral vessels to inhibit growth of melanoma and pulmonary metastases in a mammal by administering SEQ IDNO:1.

Bettan et al teach methods of treating tumors and angiogenesis (production of tumoral vessels) by electrotransfer intratumorally. Bettan et al do not speak to the nature of the gene to be introduced.

Fanslow et al teaches that disintegrin domains from a variety of ADAM proteins such as metargidin can be used to inhibit angiogenesis and endothelial cell migration (see e.g. abstract and table 1). Fanslow et al do not provide the sequences used but as evidenced by Merkulov et al, the sequence is the same as SEQ ID NO:1.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the disintegrin domain as taught by Fanslow et al and as evidenced by Merkulov et al is SEQ ID NO:1 in the methods taught by Bettan et al because Fanslow et al teach that it is within the ordinary skill of the art to use disintegrin domains of metargidin in treatment of cancer and vessel formation and because Bettan et al teach that it is within the ordinary skill of the art to target treatments by electrotransfer into the tumor. As an initial point, KSR forecloses the argument that a specific teaching, suggestion or motivation is required to support a finding of obviousness. See the recent Board decision *Ex parte Smith* --USPD2d--., slip op. at 20, (BD. Pat. App. & Interfer. June 25, 2007). In this case, it is obvious to combine known technologies with known products for predictable results and Bettan et al teach that it is known to administer treatment modalities on expression vectors encoding the product by electrotransfer and Fanslow et al teach that disintegrin domains provide successful therapeutic modalities. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Response to Amendments

Applicants response filed on 7/6/10 have been considered but are not persuasive for the following reasons. The test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the

art. See In re Keller, 642 F.2d 413,208 USPQ 871 (CCFA 1981). According to M.P.E.P. § 2143.02, "Obviousness does not require absolute predictability, however, at least some degree of predictability is required. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness. In re Rinehart. 531 F2d 1048, 189 I.JSPQ 143 (CCIPA 1976). In this case, Fanslow et al teach use of gene therapy to inhibit angiogenesis by administration of nucleic acids encoding disintegration domains but do not teach use of electrotransfer and do not teach use specifically a peptide consisting of SEQ ID NO:2. However, Batten at al teach electrotransfer methods for gene therapy and Merklov et al teach that a disintegrin domain was known to consist of the sequences of SEQ ID NO:2. Given that the methods of transfer at the time of filing embraced electrotransfer and that the art demonstrated that the disintegrin domain with SEQ ID NO:2 was known in the art.

In response to the applicant's argument, against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See In re Keller, 642 F.2d 413,208 USPQ 871 (CCPA 1981); In re Merck & Co., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Applicants have argued that Bettan et al teach a single method of transfer but do not demonstrate that this method would work with the instant gene to deliver and allow secretion. Applicants argue that Fanslow et al does not teach use of a peptide consisting of SEQ ID NO:2 and furthermore that the disintegrin domain of Fanslow et al is prepared as a fusion peptide. If, as applicants require each of these references teach what is lacking, i.e. transfer of a disintegrin coding sequence by Bettan et al or electrotransfer with a disintegrin domain of SEQ ID NO:2 then Fanslow et al or Bettan et al

would anticipate the instant claims. However, consistent with the principles of KSR, the references demonstrate that all of the instant steps are available in the art and applicable together.

> If a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability. For the same reason, if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill. Id. at ,82 USPQ2d at 1396.

When considering obviousness of a combination of known elements, the operative question is thus "whether the improvement is more than the predictable use of prior art elements according to their established functions." Id . at ___, 82 USPQ2d at 1396.

Regarding the individual arguments, applicants' argue that Bettan et al (page 10 of the response) argue to the lack of predictability of a method of electrotransfer for adequate expression of genes in gene therapy methods based upon the type of nucleic acid used. Specifically, it appears to be applicants' argument that this method is not universally applicable for any gene. However, applicants' disclosure is absent any evidence that this is the case. "The arguments of counsel cannot take the place of evidence in the record. In re Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965)." And furthermore, this statement does not appear to be supported by the art. For example, applicants own method does not involve any special steps but simply reliance on art provided methods, wherein the art does not describe an inventive step related to determining the size of DNA that will work,

> [0095] 20 .mu.g of plasmid pBi-AMEP, 10 .mu.g of plasmid Tet-off and 20 .mu.g of plasmid Tet-on were dissolved in 30 .mu.l of sterile 0.9% NaCl and injected into the tibia cranial muscle of nude or C57B1/6 mice aged 8 weeks and previously anesthetized by intraperitoneal inoculation of pentobarbital as described by Mir et al. (Mir et al., 1999). In brief, 8 electric shocks of 200 V/cm were applied for 20 ms at a frequency of 1 Hz, by means of an electrode to the mouse paw and containing two steel plates. The electrode was connected to an electropulsator PS-15 (Jouan, St Herblain, France). The same plasmids not containing the AMEP gene constituted the negative control.

In sum, applicants rely on Mir et al which teach through reference to a number of references suggesting the ease with which this phase of the method is performed. Hence, applicants' suggestion that the method of electrotransfer was part of the inventive step of the instant invention wherein the design was based upon overcoming obstacles in the art is not supported by

the available art or specification. Rather, Bettan et al teach that electrotransfer as a method can be used with predictable levels of success absent evidence to the contrary. Applicants also argue that Bettan does not teach how to successfully use the method of electrotransfer for secreted proteins. Again, there is no indication that this was an obstacle to use electrotransfer nor that applicant's inventive step is directed towards or provides means of overcoming such an obstacle.

Regarding Fanslow et al, applicants argue that use of the domain alone is not taught but rather assays a peptide that is a fusion of disintegrin and an Fc molecule. However, such an interpretation does not appear to embrace the teachings of the specification as a whole. In fact, the allowed claims for Fanslow et al include claims directed towards peptides consisting of just a disintegrin domain wherein the peptide is in a dependent claim linked to an Fc polypeptide. For example, see col 5 and claims 1 and 5,

> The present invention encompasses the use of various forms of ADAM disintegrin domains that retain at least one activity selected from the group consisting of integrin binding activity, inhibition of endothelial cell migration, and inhibition of angiogenesis. The term "ADAM disintegrin domain polypeptide" is intended to encompass polypeptides containing all or part of a native ADAM disintegrin domain, with or without other ADAM domains (such as the cysteine-rich region), as well as related forms including, but not limited to: (a) fragments, (b) variants, (c) derivatives. (d) fusion polypeptides, and (e) multimeric forms (multimers). The ability of these related forms to inhibit integrin binding endothelial cell migration, and/or inhibition of angiogenesis may be determined in vitro or in vivo by using methods such as those exemplified below or by using other assays known in the art.

> 1. A method of inhibiting angiogenesis in a mammal in need of such treatment, comprising administering to the mammal an inhibition-effective amount of an ADAM-20 disintegrin domain polypeptide, wherein the ADAM-20 disintegrin domain polypeptide comprises an amino acid sequence selected from the group consisting of: (a) amino acids 34 91 of SEQ ID NO:12; and (b) amino acids 23 305 of SEQ ID NO:12, wherein the ADAM-20 disintegrin polypeptide retains inhibition of angiogenesis activity.

> 5. The method of claim 3, wherein the multimer comprises an Fc polypeptide or a leucine zipper.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARIA B. MARVICH whose telephone number is (571)272-0774. The examiner can normally be reached on M-F (7:00-4:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, PhD can be reached on (571)-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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